Trends in the Incidence of Testicular Germ Cell Tumors in the United States

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BACKGROUND. Recent reports have suggested that the increasing rates of testicular germ cell tumors in some populations have begun to plateau. This study was conducted to examine whether rates among white men in the United States have begun to stabilize and whether rates among black men in the United States have remained low.

METHODS. Testicular germ cell tumor incidence data from in the Surveillance, Epidemiology, and End Results Program were analyzed for the years 1973–1998. Trends were examined separately for seminoma and nonseminoma. Using age-period-cohort analyses with 5-year age intervals and 5-year calendar-period intervals, changes in the slope of the trends in birth-cohort and calendar-period effects were examined.

RESULTS. Among white men, rates of seminoma continued to increase, but the rate of increase steadily declined throughout the 26-year time span. Nonseminoma rates among whites increased more slowly during the first three time intervals, then plateaued in the final interval. Rates of both seminoma and nonseminoma in black men fluctuated throughout the first three time intervals. In the final interval, the rates of seminoma increased almost 100%, whereas the rates of nonseminoma increased more modestly. Age-period-cohort modeling of the incidence data in white men found that, whereas the dominant effect was that of birth cohort, there also was a period effect.

CONCLUSIONS. Among white men in the United States, the incidence of testicular germ cell tumors varied by histology, with a continuing increase in risk only for seminoma. Among black men in the United States, the surprising increases seen between 1988 and 1998 were likely to be a calendar-period effect. ***Cancer* 2003;97: 63–70.** *Published 2003 by the American Cancer Society.**
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KEYWORDS: testicular germ cell tumor, seminoma, nonseminoma, SEER program, incidence, epidemiology.

Testicular germ cell tumors (TGCTs) comprise 98% of all testicular malignancies and are the most common type of malignancy in American men age 15–34 years.[1] Although there are a number of histologic types of TGCTs, the tumors are grouped most frequently into classic seminomas (60.6%), nonseminomas (38.8%), and spermatocytic seminomas (0.6%) for descriptive purposes. The incidence of TGCT is over five-fold greater among men in the United States of European ancestry compared with men in the United States of African ancestry, and it has been increasing among European Americans since at least 1940.[2] A similar increase in incidence has been reported among other populations of European ancestry in Europe,[3] Australia,[4] New Zealand,[5] and Canada.[6] Among these populations, it has been reported consistently that risk is affected more significantly by birth

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cohort rather than by calendar-period.[2–4,6–11] Few studies, with the exception of one by Weir et al.,[6] have reported varying patterns in incidence between seminomas and nonseminomas.

Recently, reports have suggested that the increase in incidence may be leveling off in these high-risk groups.[7,12] To determine whether the risk patterns appeared to be changing in the United States and whether the patterns of TGCT varied by histology, we examined incidence data for the years 1973–1998.

MATERIALS AND METHODS

Incidence data for TGCT were obtained from the Surveillance, Epidemiology, and End Results (SEER) Program, a population-based cancer registry system that covers approximately 10% of the United States population.[1] Only rates for classic seminoma and nonseminoma were included in the current article, because spermatocytic seminoma occurs at older ages and is considered to have few features in common with other TGCTs.[13] The SEER*Stat statistical software package[1] was used to calculate incidence rates, which were age-adjusted to the world standard population according to the method described by Segi.[14] To describe age specific trends by year of diagnosis and year of birth, rates were calculated for 5-year age groups and 5-year periods to provide a more stable estimate. Rates were plotted by calendar year of diagnosis and calendar year of birth using a logarithmic scale for the ordinate.[15]

To examine age, calendar period, and birth cohort effects simultaneously, age-period-cohort models were fitted by Poisson regression to the TGCT white incidence data by use of 5-year age and calendar-period intervals, as described previously.[16] For seminoma, there were 12 age intervals (from age 15–19 years to age 70–74 years), 5 calendar-period intervals (from 1973–1978 to 1994–1998), and 16 birth-year intervals (from 1899–1908 to 1974–1983). One calendar-period interval, 1973–1978, included 6 years; all other calendar-period intervals included 5 years. For nonseminoma, there were 10 age intervals (from age 15–19 years to age 60–64 years) and 14 birth-year intervals (ranging from 1909–1918 to 1974–1973). Each birth cohort is identified in the text by the fifth year in the interval. For example, the 1903 birth cohort refers to men who were born between 1899 and 1908.

Although interpretation of individual parameter estimates from age-period-cohort analyses can be difficult because parameters are not identifiable (i.e., there is not a unique set of estimates), a change in the slope of the birth-cohort effects curve or the calendar-period effects curve does indicate a change in the magnitude of disease rates.[16] An increase (or decrease) in the slope of the birth-cohort effects curve indicates a worsening (or moderation) in the birth-cohort pattern of risk. Such a change usually reflects a change in exposure to an etiologic factor (or factors). Changes in the slope of the lung carcinoma birth-cohort effects curve, for example, reflect changes in the prevalence of cigarette smoking.[17] An increase (or decrease) in the slope of the calendar-period effects curve indicates a worsening (or moderation) in the calendar-period pattern of risk. Such changes for cancer incidence rates usually reflect changes in diagnostic methods or changes in disease classification (i.e., coding changes).

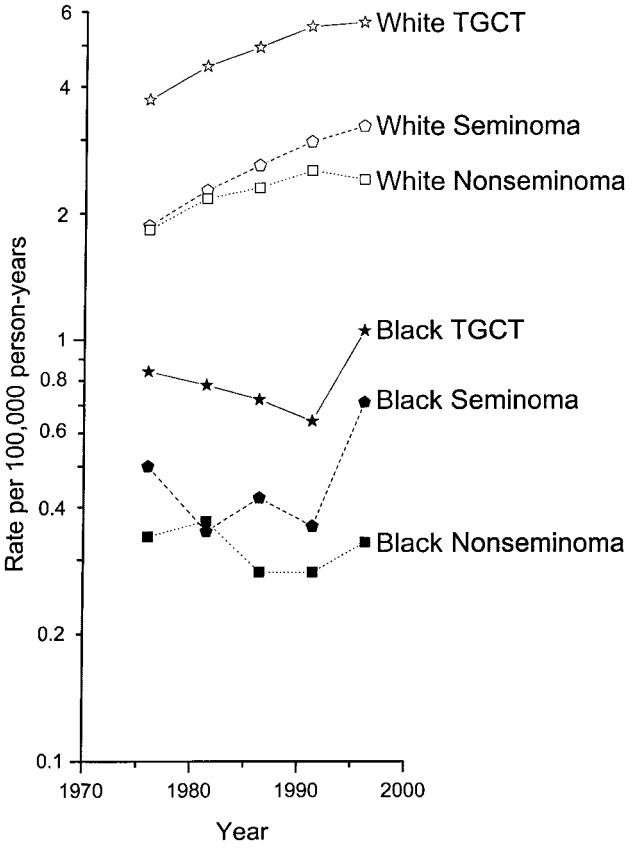

FIGURE 1. Incidence of testicular germ cell tumors (TGCTs) in the SEER Program from 1973–1978 to 1994–1998.

RESULTS

The overall incidence of TGCT rose over 44% from 3.35 per 100,000 population to 4.84 per 100,000 men between 1973–1978 and 1994–1998. Although the rates increased among both white men and black men, the increases were qualitatively different in each group (Fig. 1). Among white men, the incidence rose 52% from 3.69 per 100,000 men in 1973–1978 to 5.62 per 100,000 men in 1994–1998. The increase in incidence rates between two successive 5-year intervals, how-

TABLE 1
Change in Incidence Rate of Testicular Germ Cell Tumors: SEER Program, 1973–1978 to 1994–1998

Interval	No. of TGCTs in later period	Change in rate (%)			Seminoma as % of TGCTs in later period
		TGCT	Seminoma	Nonseminoma	
White men					
1973–1978	1945	—	—	—	50.3
1973–1978 to 1979–1983	2249	+ 20.60	+ 21.39	+ 18.58	50.8
1979–1983 to 1984–1988	2665	+ 10.11	+ 14.54	+ 5.99	54.2
1984–1988 to 1989–1993	3082	+ 12.24	+ 13.85	+ 10.00	57.1
1989–1993 to 1994–1998	3183	+ 2.18	+ 8.78	− 4.74	60.9
1973–1978 to 1994–1998	13,124	+ 52.30	+ 72.19	+ 31.69	—
Black men					
1973–1978	42	—	—	—	59.5
1973–1978 to 1979–1983	45	− 13.25	− 30.00	+ 8.82	48.8
1979–1983 to 1984–1988	46	− 2.78	+ 20.00	− 24.32	57.8
1984–1988 to 1989–1993	47	− 8.57	− 14.29	± 0.00	57.4
1989–1993 to 1994–1998	84	+ 62.50	+ 97.22	+ 17.86	71.1
1973–1978 to 1994–1998	264	+ 25.30	+ 42.00	− 2.94	—

SEER: Surveillance, Epidemiology and End Results; TGCTs: testicular germ cell tumors.

ever, fell throughout the period (Table 1). For example, whereas the incidence increased by > 20% from 1973–1978 to 1979–1983, the rate of increase was only slightly greater than 2% between 1989–1993 and 1994–1998. The final increase was not statistically significant ($Z = 0.99$; $P = 0.32$), whereas the previous three increases were significant. Among black men, the overall incidence of TGCT rose 25% from 0.83 per 100,000 men in 1973–1978 to 1.04 per 100,000 men in 1994–1998. Unlike the trend in white men, however, the incidence rate of TGCT in black men declined during the first three periods. The rate increased (62%) only in the final period between 1989–1993 and 1994–1998. This increase was statistically significant ($Z = 2.67$; $P = 0.008$), unlike the declines in the previous three periods.

An examination of the trends by histologic type found that seminoma and nonseminoma had distinguishable incidence patterns in both racial groups (Fig. 1). Among white men, the incidence of seminoma increased 72% overall, although the rate of increase, like total the TGCT rate, declined in each successive time interval (Table 1). Unlike the total TGCT rate, however, the increase in the final interval was statistically significant ($Z = 2.45$; $P = 0.014$). In contrast, the incidence of nonseminoma in white men, although it showed an overall rate increase of 31.7%, grew at a slower rate compared with seminoma throughout the first three time intervals and then declined nonsignificantly in the final interval. Due to the diverging rates of seminoma and nonseminoma over time, the seminoma: nonseminoma ratio went from 50:50 in 1973–1978 to 60:40 by 1994–1998.

Among black men, the incidence of seminoma rose 42% overall, principally due to a near 100% statistically significant increase ($Z = 3.07$; $P = 0.002$) in the final time interval (Fig. 1). In contrast, the incidence of nonseminoma fluctuated throughout the time span and ended slightly lower (− 2.9%) compared with the incidence in 1973–1978. Notably, however, the rate of nonseminoma increased in the final interval between 1989–1993 and 1994–1998, although the increase did not attain statistical significance ($Z = 0.54$; $P = 0.59$) (Table 1). The seminoma: nonseminoma ratio among black men went from 60:40 in 1973–1978 to 70:30 by 1994–1998.

The age specific seminoma incidence rates for white men are shown in Figure 2A for all age groups and in Figure 3A for the high-risk age groups (age 15–49 years). The age specific rates rose over time in all high-risk age groups (from age 15–19 years to age 45–49 years) from a minimum of 60% (from 3.25 to 5.21 per 100,000 men) in the group age 45–49 years to a maximum of 117% (from 4.57 to 9.92 per 100,000 population) in the group age 30–34 years. The peak age of incidence remained 30–34 years throughout the time span, with the exception of the earliest time interval, when the rate was slightly higher among the group age 35–39 years (5.09 per 100,000 men) compared with the group age 30–34 years (4.57 per 100,000 men).

The age specific nonseminoma incidence trends for white men are shown in Figure 2B. It can be seen by comparing the age specific seminoma curves (Fig. 2A) that nonseminoma differed in that it had an early minor peak in the group age 00–04 years and in that it

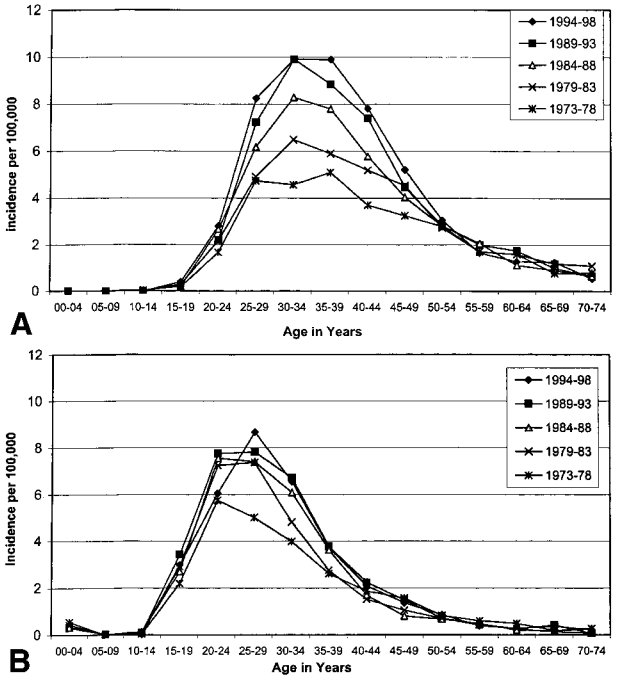

FIGURE 2. Age specific incidence of seminoma and nonseminona among white males. Data from the SEER Program, 1973–1978 to 1994–1998. (A) Seminoma in white men: SEER Program, 1973–1978 to 1994–1998. (B) Nonseminoma in white men (data from the SEER Program, 1973–1978 to 1994–1998).

started to increase to its major peak at an earlier age (15–19 years) compared with seminoma. In addition, increases in incidence rates over time in the high-risk age groups for nonseminoma were more modest compared with seminoma (Fig. 3B). Overall, the group age 25–29 years experienced the greatest increase (72%; from 5.02 to 8.67 per 100,000 men), whereas, in contrast, the group age 44–49 years experienced a small decline (−12%; from 1.57 to 1.37 per 100,000 men). All age groups, except for the group age 25–29 years, saw their rates decline in the most recent time interval. Over the 26-year time span, the peak age of nonseminoma incidence shifted from the group age 20–24 years to the group age 25–29 years.

Among black men, the age specific rates of seminoma and nonseminoma (data not shown) were very unstable due to the small number of tumors in each group (Table 1). However, seminoma rates rose in all age groups except for the group age 25–29 years, in which there was a 30% decline. The greatest increase was in the group age 35–39 years (153%), which has also been the peak incidence group since 1984. All age groups except the group age 15–19 years experienced an increase in rates between the final two time intervals. The rates of nonseminoma in black men fell in 5

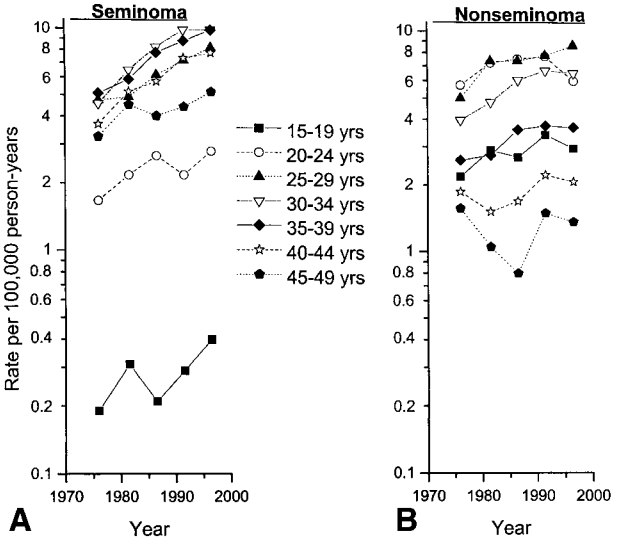

FIGURE 3. Incidence of testicular germ cell tumors by age (data from the SEER Program, 1973–1978 to 1994–1998).

of the 7 age groups, rising only in the group age 15–19 years (300%) and in the group age 25–29 years (114%). Like the white men, the group age 25–29 years was the peak incidence group for the black men.

The geographic distribution of TGCTs by SEER registry in white men changed little over time. Throughout the entire time span, the highest rates occurred in 3 western region registries: Hawaii, Seattle, and San Francisco/Oakland, where the rates ranged between 6.00 and 7.13 per 100,000 men in the 1994–1998 interval. In contrast, the rates in the other 6 registries ranged between 4.39 and 5.71 per 100,000 men. Among black men, there was a great deal of fluctuation in rates due to small numbers. In the final time interval, Atlanta, Detroit, and San Francisco/Oakland had higher rates, ranging between 1.14 and 1.31 per 100,000 men, compared with the other 6 registries, where the rates ranged from 0.0 to 0.58 per 100,000 men.

Estimates of the birth-cohort and calendar-period effects for seminoma in white men are shown in Figure 4. The birth-cohort effects curve shows clear, statistically significant ($P < 0.0001$) evidence of an increase in slope around 1940 (i.e., the slope is negative prior to 1933 and is positive after 1943, giving the curve a convex shape). The calendar-period effects curve is slightly concave, suggesting that there was a consistent moderation of calendar-period risk over the study interval. Thus, there is no evidence that the secular increase in seminoma rates in white men is due to increased detection, and the increase appears to be explained by changes in exposure to etiologic factors.

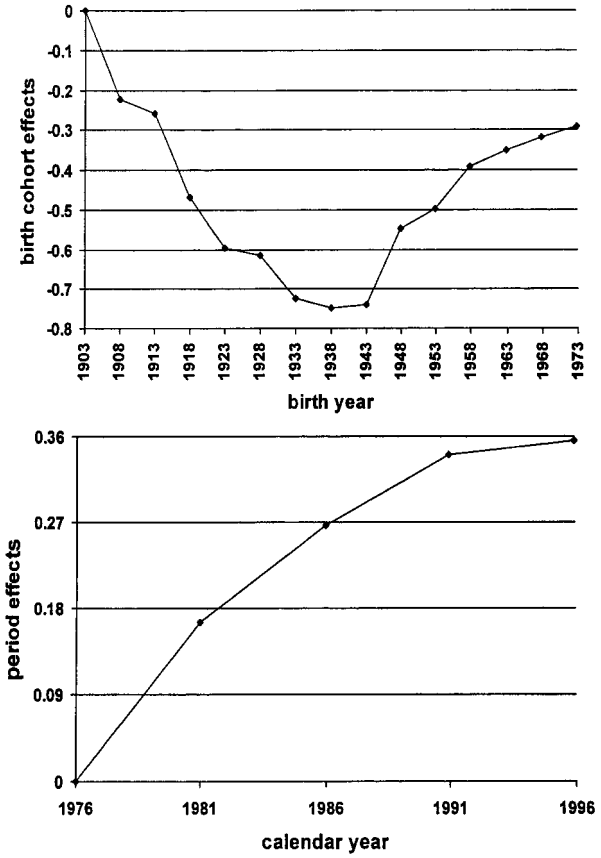

FIGURE 4. Maximum likelihood estimates of 10-year birth cohort effects (top) and 5-year calendar period effects (bottom) for an age-period-cohort model fit to seminoma incidence data for white men in the United States age 15–74 years (data from the SEER Program, 1973–1998).

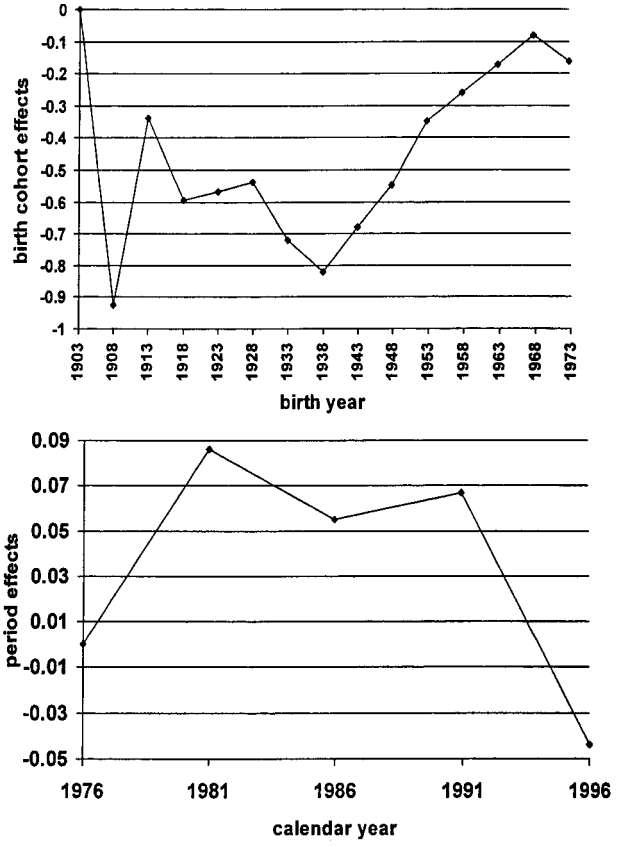

FIGURE 5. Maximum likelihood estimates of 10-year birth cohort effects (top) and 5-year calendar period effects (bottom) for an age-period-cohort model fit to nonseminoma incidence data for white men in the United States age 15–74 years (data from the SEER Program, 1973–1998).

The birth-cohort effect curves and calendar-period effect curves for nonseminoma in white men are shown in Figure 5. Although the early birth-cohort effects are somewhat variable because of the low rates in older men, the birth-cohort effects curve for nonseminoma is consistent with an increase in slope around 1940 ($P = 0.009$). The calendar-period effects curve also is somewhat more variable for nonseminoma than for seminoma, but it has a generally concave shape, as was the case for seminoma. Thus, the secular increase in nonseminoma rates in white men also appears to reflect changes in exposure to etiologic factors.

DISCUSSION

Among all men in the United States, the incidence of TGCT rose 44% between 1973 and 1998. The incidence of seminoma rose almost 64%, however, whereas the incidence of nonseminoma rose only 24%. These data and the trends by histology over time indicate that different patterns for different TGCT types may be emerging. Among white men, the rate of seminoma increased throughout the time span, although the rate of increase steadily declined with each 5-year time interval. The rate for nonseminoma, by contrast, rose more slowly compared with the rate for seminoma during the first three intervals and then plateaued in the final interval. In black men, the patterns were quite different compared with the patterns in white men. The rates for both seminoma and nonseminoma fluctuated throughout the first three intervals. In the final interval, however, the rate for seminoma almost doubled, whereas the rate for nonseminoma rose more modestly.

Although we observed calendar-period effects on the risk of both seminoma and nonseminoma in white men, the dominant effect was that of birth cohort, as reported in other populations.[2–11] The evidence of a period effect as well as a birth-cohort effect has been described less frequently. Zheng et al.[2] reported a period effect for seminoma, but not for nonseminoma,

in Connecticut. In contrast, Moller[7] reported a significant period effect, indicative of an attenuation of risk, on total TGCT rates in Denmark and noted that the effect was especially pronounced in the interval of 1990–1995. Like Moller, we saw evidence of a consistent moderation of calendar-period risk, although the recent decrease in slope appeared in Denmark slightly earlier than in the United States. It is possible that Zheng and colleagues[2] did not detect a period effect for nonseminomas because the data in their report only extended to 1992.

The diverging patterns in the incidence of seminoma and nonseminoma that we noted were somewhat unanticipated. With the exception of the report by Weir et al.,[6] the majority of prior reports have not found varying patterns in the incidence of TGCT by histology. Weir et al. reported that the incidence of TGCT had risen in Ontario, Canada, by almost 60% between 1964 and 1996. When analyzing by histologic type, Weir et al. found that the rates of both seminoma and nonseminoma had increased during the interval, although the rate of seminoma increased by 72%, whereas the rate of nonseminoma rose by only 45%. These increases are very similar to the increases among the white population in the United States, where the overall increase was 52%, the increase in seminoma was 72%, and the increase in nonseminoma was almost 32%. Weir et al. also reported that the rates of nonseminoma had been declining in the youngest age groups (age 15–29 years) since the early 1990s. We saw this same trend among the white population in the United States, in which the rates of nonseminoma declined in all age groups, except for the group age 25–29 years, between the final two periods (1989–1993 and 1994–1998).

Divergent trends in seminoma and nonseminoma may be consistent with a number of explanations, including changes in diagnostic patterns, changes in coding practices, and changes in primary risk factors. There is little evidence to suggest, however, that changes in diagnostic patterns have occurred between 1973 and 1998. There is no population screening for TGCT in the United States; thus, the great majority of patients present with clinical symptoms. The exception to this, however, is the group of men who are diagnosed due to intensified follow-up after a previous TGCT diagnosis. Second TGCTs occur in only about 5% of men with a prior diagnosis and, thus, are unlikely to explain trends at the population level. Similarly, changes in coding over time are not likely to explain the greater increase of seminoma compared with nonseminoma. Although the switch in coding from the International Classification of Diseases for Oncology, first edition (ICD-O-1) to ICD-O-2 in 1990 introduced a code for mixed germ cell tumors, these tumors would continue to be classified as nonseminomas both before and after the introduction of ICD-O-2.[18]

A third possibility is that there have been changes in the prevalence of risk factors over time. The data we report would suggest that there are either somewhat different risk factors for seminoma and nonseminoma or that the histologic type of TGCT is related to the intensity of exposure of common risk factors. Although not all studies have found differences in risk factors by histology,[19] some studies have reported histologic specific risks. Akre et al.[20] found that indicators of higher pregnancy estrogens in mothers, such as increased maternal age, increased placental weight, and decreased parity, had a stronger association with seminoma compared with nonseminoma among sons. The association of seminoma with increased maternal age also was reported by Swerdlow et al.,[21] Sabroe and Olsen,[22] and Moller and Skakkebaek.[23] It has been reported that low birth order has a stronger association with seminoma compared with nonseminoma by Prener et al.,[24] Swerdlow et al.,[21] and Sabroe and Olsen.[22] Although cryptorchism is related significantly to total TGCT in the vast majority of studies, several studies have found higher risks for seminoma compared with nonseminoma.[25–27] Prematurity[23] and early age at hernia repair[28] also reportedly increase the risk of seminoma. In general, the trends in prevalence of most of these factors are consistent with an increased risk of seminoma since 1940. For example, parity has decreased among women in the United States, and age at first birth has increased since World War II.[29] During the same time span, the survival of premature infants has improved significantly,[30] thus perhaps increasing the likelihood of seminoma as a sequelae. Trends in the incidence of cryptorchism during the period of interest are difficult to evaluate; however, some evidence suggests that rates have increased in the United States since 1970.[31]

Fewer variables have been associated preferentially with nonseminoma, perhaps because nonseminoma is a heterogeneous mix of several histologic types, including types with both seminomatous elements and nonseminomatous elements. However, Akre et al.[20] found that nonseminoma was associated more closely than seminoma with variables indicative of intrauterine growth retardation, i.e., low birth weight and decreased maternal age. Sabroe and Olsen[22] also found that low birth weight had a stronger association with nonseminoma. Both Stone et al.[25] and Coupland et al.[27] reported a correlation between trauma and nonseminoma. In addition, Coupland et al. found an association with history of sexually trans-

mitted diseases and an inverse association with late puberty. In accordance with this observation, Moss et al.[32] reported an increased risk of nonseminoma with early puberty. It is difficult to know whether the prevalence of any of these variables has changed enough over time to explain a plateauing incidence of nonseminoma. However, at least one variable, maternal age, has increased rather than decreased in the United States, thus perhaps shifting the risk toward seminoma and away from nonseminoma.[29]

It is conceivable, of course, that seminoma and nonseminoma share most risk factors and that seminoma has not yet experienced a plateauing effect because of the relatively recent introduction of a new seminoma specific risk factor into the population. Although it is unclear what such a risk factor may be, an increased risk of seminoma has been reported by some investigators among men infected with human immunodeficiency virus (HIV).[33] The earliest report of TGCT in patients with acquired immunodeficiency syndrome occurred in 1985,[34] the middle of the decade in which the trends of seminoma and nonseminoma began to diverge. It is still unclear, however, whether HIV, which affects a very small proportion of the total population, may be influencing the risk of TGCT at the population level.

One of the most intriguing aspects of TGCT epidemiology in the United States has been the disparity in incidence rates between white men and black men. Although the rates in black men have remained strikingly lower compared with the rates in white men, we found that, in the final time interval, black men had experienced a noticeable increase in the incidence of seminoma and, to a much lesser extent, an increase in nonseminoma. There were insufficient numbers of patients with TGCT among black men to allow inferences based on a formal age-period-cohort analysis. The trends in incidence rates for black men, however, are shown for two broad age groups in Figure 6. For both younger men (age $<$ 40 years) and older men (age $\geq$ 40 years), there was an increase in the slope of the incidence rate curve in the final calendar period. This suggests that the recent increase in TGCT incidence among black men is primarily a calendar-period phenomenon. Calendar-period effects usually reflect changes in detection or coding rather than changes in the prevalence of risk factors, although there is little evidence of either increased detection or coding changes. Furthermore, the calendar-period effects curve for white men showed a moderation in risk in the final period; thus, the recent increase among black men may be explained by increased detection only if there was a screening program specifically targeting black men. Due to the rarity of the tumor in

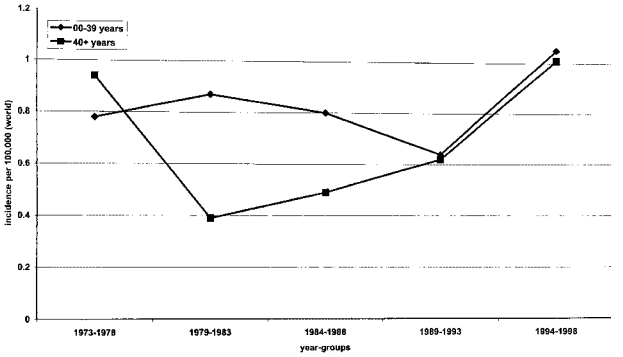

FIGURE 6. Incidence of testicular germ cell tumors in black men (data from the SEER Program, 1973–1998 to 1994–1998).

black men, there is also very little in the literature concerning differences in risk factors between black men and white men.

In summary, the incidence rate of TGCT has continued to increase among men in the United States, although the pace of the increase has slowed over time. Different patterns in seminomas and nonseminomas also may be emerging. The incidence of nonseminomas may have leveled off in the most recent time interval, whereas the incidence of seminoma continued to increase. Although the rates among white men remain substantially higher compared with the rates among black men, an unexpected recent increase in rates, particularly of seminoma, among black men is notable. Future investigations would do well to examine causes for the increase in TGCT among black men and the reasons for the variable patterns in risk between black men and white men.

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